PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PN0302-PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/NO2004/000002	International filing date *(day/month/year)* 09.01.2004	Priority date *(day/month/year)* 09.01.2003
International Patent Classification (IPC) or national classification and IPC A61K51/04, A61K49/08, A61K49/00		
Applicant AMERSHAM HEALTH AS et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.08.2004	07.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Gonzalez Ramon, N Telephone No. +31 70 340-3466

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000002

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-27 as originally filed

   Claims, Numbers

   1-10 as originally filed

   Drawings, Sheets

   1/1 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000002

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-10 in part

because:

☒ the said international application, or the said claims Nos. 9, 10 in relation to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-10 in part

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000002

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,4
	No:	Claims	1, 2, 5-10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	see separate sheet
	No:	Claims	siehe Beiblatt

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 9, 10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

In the present application, the International Searching Authority has restricted the search under the following objections under Articles 5 and 6 PCT:

Present claim 6 does not comply with Art 5 PCT.

No support is to be found in the present application for a contrast agent wherein the imaging moiety comprises the compounds listed on claim 6: 90Y, 47Sc, 51Cr, 177mSn, 67Cu, 167Tm, 97Ru, 188Re, 177Lu, 203 PB, 141Ce.

The imaging moieties effectively described refer only to the listed in page 5 third paragraph and page 7, as well as the examples.
No further disclosure is to be found in the present application for the above imaging moieties claimed (Art 5 PCT).

Moreover the subject matter of present claims 1-10 does not meet the requirements of Articles 6 PCT and Art 5 PCT for the following reasons:

Present claims 1-10 relate to compounds/methods defined by reference to vague characteristics or properties, namely "non-peptidic vector having affinity for the angiotensin II receptor", " a spacer", "a linker moiety", "a moiety detectable in an in vivo imaging procedure" (claim 1); "radionuclide", "paramagnetic metal ion", "fluorescent metal ion", "chromophores", "heavy metal ions", "cluster ions" (claim 5).

The claims cover all compounds/methods having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds/methods.

Support is only to be found in the present application for those parts relating to the compounds as described in the examples and those specifically disclosed by chemical

name in claims 2-4, 6 in relation to their use as contrast agents.

Moreover claims 1, 3-10 encompass a genus of compounds defined only by their function, namely " non-peptidic vector having affinity for the angiotensin II receptor" wherein the relationship between the structural features of the members of the genus and said function have not been defined.

In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the described assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed.

It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. Therefore, claims 1, 3-10 do not fulfil the requirements of Art. 5 and Art. 6 PCT.

No opinion will be formulated by the ISA in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 9, 10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The applicant's attention is drawn to the fact that the present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up.

The following documents (D) are referred to in this communication

D1 : WO 98/18496 A

D2 : WO 01/92283 A
D3: JP09165378
D4 : WO 01/77145 A
D5 : WO 02070018 A

Novelty (Article 33 (1) PCT)

The subject-matter of present claims 1, 2, 5-10 is not novel in the sense of Article 33 (1) PCT.

The reasons therefore are the following:

D1, (document cited by the applicant) discloses: Contrast agent composition of formula V-L-R wherein V is an organic group with binding affinity for angiotensin II receptor site (including losartan, PD 123177 and imidazoles) (see page 10), L is a linker or a bond and R is a reporter moiety including chelated metal species of paramagnetic metal ion or metal radionuclide (90Y, 99mTc, 111In, 47Sc, 67Ga, 51Cr, 177Sn, 67Cu, 167Tm, 97Ru, 188Re, 177Lu, 199 Au, 203Pb and 141Ce) or fluorescent metal ions (see page 5-9; page 46-47; claims 6, 10-12).
Consequently the subject matter of present claims 1, 2, 5-10 is not novel over D1.

D2 discloses cobalamine compounds linked to a cardiovascular agent including atacand (namely candesartan), cozaar (namely losartan) and diovan (namely valsartan) and a chelated detactable radionuclide (141Ce, 51Cr, 111In, 199Au, 177Lu, 188Re, 99mTc, 90Y) as imaging agents in the treatment or diagnosis of cardiovascular disease,
therefore rendering the subject matter of present claims 1, 2, 5-10 not novel.

D3 discloses imidazole compounds having angiotensin II receptor antagonizing action comprising a 18F group for positive electron radiation tomography (see abstract).
Consequently the subject matter of present claims 1, 5-10 is not novel over D3.

Inventive step (Article 33 (2) PCT)

The subject matter of present claims 1-10 cannot be considered as involving an inventive step for the following reasons:

The problem to be solved by the present application is the detection of diseases and disorders such as heart failure, atherosclerosis and restricted blood flow, vascular diseases and diseases where fibrosis is prominent as well as to monitor the progression of treatment for such diseases (page 3, paragraph 5).

The solution proposed is the use of a contrast agent of formula V-L-Z wherein V is a non-peptidic vector having affinity for the angiotensin receptor II, L is a bond, a spacer

or a linker moiety and Z represents a moiety detectable in an in vivo imaging procedure.

Previously discussed document D1, which can be considered the closest prior art discloses contrast agent compositions of formula V-L-R wherein V is an organic group with binding affinity for angiotensin II receptor site (including losartan, PD 123177 and imidazoles), L is a linker or a bond and R is a reporter moiety including chelated metal species of paramagnetic metal ion or metal radionuclide (90Y, 99mTc, 111In, 47Sc, 67Ga, 51Cr, 177Sn, 67Cu, 167Tm, 97Ru, 188Re, 177Lu, 199 Au, 203Pb and 141Ce) or fluorescent metal ions.

The difference between D1 and the subject matter of claims 3, 4 of present application is the fact that the particular chelating agent of Formula II as depicted in claim 3 or formula e as depicted in claim 4 is not effectively disclosed by this document.

However the skilled man, well aware that said known claimed chelating agents and in particular pn 216 (the preferred dioxime chelating agent of the present application encompassed under present claims 3, 4) provide contrast enhancement in diagnostic imaging techniques as described inter alia in D4 and D5 (see passages cited on search report), would have easily applied the teaching of D1 to the use of the particular chelating agents claimed.

Consequently such solutions cannot be considered as involving an inventive step but as providing equivalent alternatives of contrast agents which are obvious for the skilled person only relying on know properties of known compounds.

Therefore the subject matter of claims 1-10 cannot be considered as involving an inventive step.